Acute endothelin A receptor antagonism improves pulmonary and systemic haemodynamics in patients with pulmonary arterial hypertension that is primary or autoimmune and related to congenital heart disease

CONGENITAL HEART DISEASE

Acute endothelin A receptor antagonism improves pulmonary and systemic haemodynamics in patients with pulmonary arterial hypertension that is primary or autoimmune and related to congenital heart disease

S C Apostolopoulou, S Rammos, Z S Kyriakides, D J Webb, N R Johnston, D V Cokkinos, D Th Kremastinos

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See end of article for authors' affiliations

Correspondence to: Dr Sotiria C Apostolopoulou, Department of Paediatric Cardiology, Onassis Cardiac Surgery Centre, 356 Syngrou Avenue, Athens GR 176 74, Greece; riapos@hol.gr

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Objective: To evaluate the acute haemodynamic effect of BQ-123, a selective endothelin A receptor antagonist, in severe chronic pulmonary arterial hypertension (PAH) of primary or autoimmune origin or related to congenital heart disease.
Design: Prospective open clinical study.
Setting: Cardiology tertiary referral centre.
Patients: 26 patients with chronic PAH were studied, with mean (SEM) age 29 (3) years (range 4–71 years), mean pulmonary artery pressure 68 (4) mm Hg, and pulmonary vascular resistance index 1694 (170) dyne·s·cm^{-5}. Patients were divided in three groups according to PAH aetiology: primary or autoimmune PAH (n = 12), and PAH associated with congenital heart defects with (n = 6) or without (n = 8) complete mixing.
Intervention: BQ-123 200 nmol/min was infused for 60 minutes in the right atrium with sequential haemodynamic measurements at 30 minute intervals.
Results: BQ-123 improved mean pulmonary artery pressure from 68 (4) to 64 (4) mm Hg ($p < 0.05$), pulmonary vascular resistance index from 1694 (170) to 1378 (145) dyne·s·cm^{-5} ($p < 0.001$), pulmonary cardiac index from 3.0 (0.2) to 3.4 (0.3) l/min/m^2 ($p < 0.001$), and effective cardiac index from 2.5 (0.2) to 2.7 (0.2) l/min/m^2 ($p < 0.01$). Haemodynamic response was similar in all groups except for systemic cardiac index where a different ($p = 0.0001$, $F = 5.53$) response was observed; systemic cardiac index increased from 2.7 (0.2) to 2.9 (0.2) l/min/m^2 ($p < 0.001$) when patients with complete mixing were excluded, in whom systemic cardiac index tended to decrease from 3.4 (1.0) to 3.0 (0.6) l/min/m^2 ($p = 0.06$).
Conclusions: Acute endothelin A receptor antagonism induces substantial haemodynamic improvement in severe chronic PAH of primary or autoimmune origin or related to congenital heart disease.

Pulmonary arterial hypertension (PAH) is a rare disease with diverse pathophysiological mechanisms, an often challenging management, and a poor prognosis. The overall one year survival from diagnosis for patients with primary PAH who do not respond to vasodilatators, such as calcium channel blockers or epoprostenol, is 60–70%,[1] while responders to vasodilatators have better survival.[2] Indices of right heart failure, such as increased right atrial pressure and decreased cardiac index, are associated with reduced survival, both in the adult[2] and in the paediatric populations.[3] Irreversible PAH results from vascular remodelling with narrowing and obliteration of pulmonary arteries, but the molecular mechanisms underlying this process are unknown. Endothelin (ET) 1 is an endothelium derived peptide, which exerts profound vasoconstriction through action on ET_A and ET_B receptors on smooth muscle cells and vasodilatation through action on ET_B receptors on endothelium, leading to prostacyclin and nitric oxide release.[4] Patients with PAH may have increased plasma ET-1 concentrations[5] and greatly increased ET-1 expression in vascular endothelial cells of the pulmonary bed.[6] Endothelin converting enzyme inhibition[7] and endothelin receptor antagonism (ERA)[8] protect from the development of PAH or ameliorate existing PAH in animal models.[9] More recent human studies with ERA show improvement in pulmonary and systemic haemodynamics in patients with heart failure[10] and infants with PAH after congenital heart surgery in a small study, which also reported potentially adverse effects from ERA use in the acute postoperative period.[11] ERA with the dual receptor antagonist bosentan has been shown to be beneficial in patients with primary or autoimmune PAH, both acutely in a small study[12] and chronically in a larger study in which ERA improved exercise capacity, dyspnoea index, and functional class, while increasing the time to clinical worsening.[13] A recent study[14] showed improvement in cardiopulmonary haemodynamics and exercise capacity with the ET_A receptor antagonist sitaxsentan in a mixed PAH population without separate analysis of haemodynamic response in the various subgroups.

The purpose of this study was to evaluate the effect of continuous short term ET_A receptor antagonism on the haemodynamic condition of patients with severe chronic PAH of diverse aetiology: primary, autoimmune, and PAH related to congenital heart disease, with emphasis on detailed analysis of the haemodynamic response depending on the presence and degree of pulmonary and systemic circulation mixing.

Abbreviations: ERA, endothelin receptor antagonism; ET, endothelin; PAH, pulmonary arterial hypertension

Table 1 Clinical data

Patient	Group	Diagnosis	Age (years)	Sex	Symptoms	Medications	NYHA
1	1	Primary PAH	46	M	DOE	Nifedipine, warfarin	II
2	1	Primary PAH	24	F	DOE	Nifedipine, warfarin	II
3	1	Primary PAH	32	F	DOE	Furosemide, captopril	II
4	1	Primary PAH	27	F	DOE	Warfarin	II
5	1	Primary PAH	39	F	DOE	Nifedipine	II
6	1	Primary PAH	31	M	DOE, leg oedema	Nifedipine, warfarin, digoxin, furosemide	IV
7	1	Primary PAH	35	F	DOE, syncope	Furosemide	II
8	1	Primary PAH	26	M	DOE	Furosemide	II
9	1	PAH, cold agglutinin syndrome	50	M	DOE, syncope	Nifedipine, warfarin, furosemide	IV
10	1	PAH, CREST syndrome	71	M	DOE	Nifedipine, furosemide	II
11	1	PAH, systemic lupus erythematosus	38	F	DOE, leg oedema	Warfarin, furosemide, solumedrol	III
12	1	PAH, systemic lupus erythematosus	25	F	DOE	Warfarin, solumedrol, endoxan	II
13	2	PAH, secundum ASD	27	F	DOE, cyanosis	Nifedipine, warfarin, digoxin	III
14	2	PAH, secundum ASD	32	F	DOE, cyanosis	Warfarin	II
15	2	PAH, ASD repair at 7 years	17	F	DOE, cyanosis	Furosemide	III
16	2	PAH, VSD repair at 7 years, ASD	26	M	DOE, cyanosis, syncope, paroxysmal atrial flutter	Warfarin, digoxin, furosemide, amiodarone	III
17	2	PAH, arterial switch at 2 weeks	8	M	Mild DOE	None	II
18	2	PAH, PDA closure at 6 years	17	F	DOE, chest pain	Nifedipine, warfarin	III
19	2	PAH, PDA closure at 15 years	46	F	DOE, chest pain	Nifedipine, warfarin	IV
20	2	PAH, ASD repair at 45 years	46	M	DOE, oedema	Nifedipine, warfarin, digoxin, furosemide	III
21	3	PAH, double inlet single left ventricle	12	F	DOE, cyanosis	None	II
22	3	PAH, double inlet single left ventricle	5	F	DOE, cyanosis	Furosemide, digoxin, captopril	II
23	3	PAH, double outlet right ventricle	39	M	DOE, cyanosis	Furosemide, aspirin	II
24	3	PAH, truncus arteriosus, restrictive ASD	4	M	DOE, cyanosis	Digoxin, furosemide	II
25	3	PAH, aortopulmonary window	29	F	DOE	None	II
26	3	PAH, aortopulmonary window	12	M	DOE, cyanosis	None	II

Group 1: primary or automimmune pulmonary arterial hypertension (PAH); group 2: PAH associated with congenital heart disease without complete mixing; group 3: PAH associated with congenital heart disease with complete mixing.
ASD, atrial septal defect; CREST syndrome: calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, and telangiectasias; DOE, dyspnoea on exertion; F, female; M, male; NYHA, New York Heart Association functional class; PAH, pulmonary arterial hypertension; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

PATIENTS AND METHODS

Patient population

Twenty six patients (11 male and 15 female patients) with severe chronic PAH were enrolled in this study between May 1998 and May 2000 at our institution. Table 1 describes the patients' baseline clinical characteristics. In a predetermined way, for the purpose of later analysis, the patients were divided in three groups: group 1, with primary or autoimmune PAH (n = 12); group 2, with PAH associated with congenital heart disease without complete mixing (n = 8); and group 3, with PAH associated with uncorrected congenital heart disease with complete mixing, as in Eisenmenger syndrome (n = 6). Mean (SEM) age at study was 29 (3) years (range 4–71 years, median 28 years). Patients 13 and 14 had atrial shunts and patients 21–26 had complete mixing lesions with unrestrictive communications between the systemic and pulmonary circulation and increased pulmonary vascular resistance that precluded surgical correction.

All patients, excluding the preschool patients, underwent a complete cardiopulmonary evaluation including physical examination, ECG, chest radiograph, echocardiogram, lung perfusion scan, and treadmill exercise stress test (Dargie protocol).

Study protocol

The study protocol was approved by the institutional review committee and was conducted according to institutional guidelines after written informed consent was obtained. Cardiac catheterisation was performed under local anaesthesia with additional intravenous midazolam for the four younger patients. Pulmonary arterial, right atrial, and pulmonary capillary wedge pressures were recorded with an end hole balloon catheter (Swan-Ganz catheter) and systemic pressures were obtained with a pigtail catheter. Systemic and pulmonary arterial and venous saturations were obtained to calculate cardiac outputs with the Fick principle using table derived assumed oxygen consumption values.[15] The transpulmonary pressure gradient was defined as the difference between mean pulmonary artery and mean pulmonary capillary wedge or left atrial pressures. Pulmonary and systemic vascular resistance indices were calculated by the standard formula.[16] In no case was carbon dioxide raised above 42 mm Hg, thus contributing to the increased pulmonary artery pressure or resistance. During baseline evaluation, blood samples for ET-1 and BQ-123 measurements were obtained from the right atrium, pulmonary artery, and aorta and stored at –70°C after rapid centrifugation until assay.

All patients underwent continuous infusion of the highly selective ET_A antagonist BQ-123 (*cyclo*(-D-asp-L-pro-d = val-L-leu-D-trp-), Clinalfa, Läufelfingen, Switzerland) for 60 minutes in the right atrium. Adult patients received 200 nmol/min and paediatric patients received 100 nmol/min/m^2, based on previous studies.[11] The above dose was selected because it has been proved to be truly selective for the ET_A receptor.[17] Haemodynamic evaluation and site sampling were repeated at 30 and 60 minutes of the infusion and 30 minutes after the end of the infusion.

Plasma ET-1 concentrations were determined by standard radioimmunoassay (Peninsula Laboratories Europe, St Helens, UK), as previously described.[18] BQ-123 concentrations in plasma were measured by high performance liquid chromatography with fluorescence detection, as previously described.[17]

The descriptive data are presented as the mean (SEM). Statistical analysis of the data was performed with repeated measures analysis of variances, followed by post hoc analysis with Tukey's test; differences were considered significant for $p < 0.05$.

RESULTS

Excluding the patients with uncorrected congenital heart disease, echocardiograms showed dilatation of the right atrium and ventricle with end diastolic diameter 2.8–5.5 cm in the parasternal short axis view. There was moderate to severe

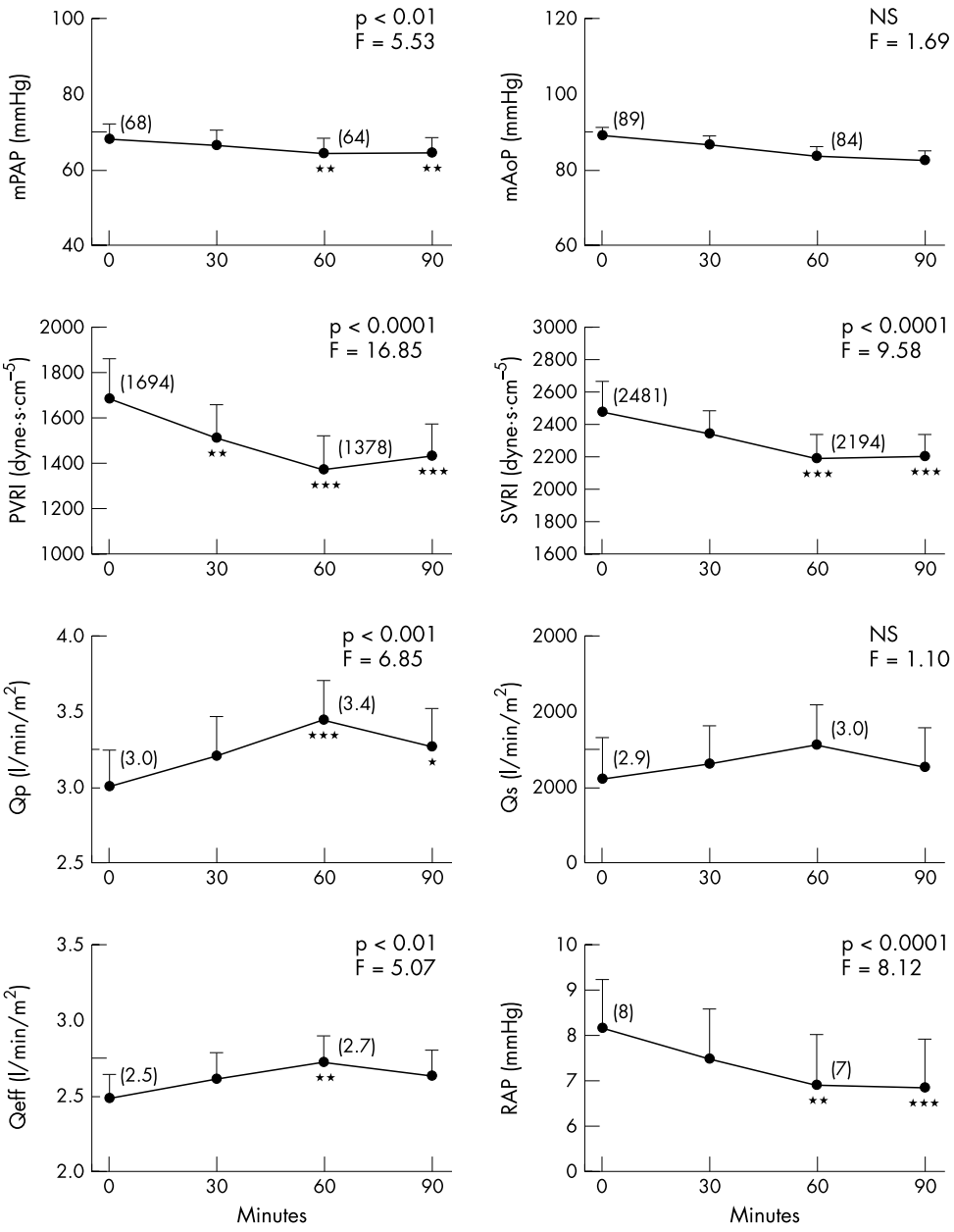

Figure 1 Haemodynamic effects over time of BQ-123 administration in the total patient cohort. The three groups responded similarly in all haemodynamic variables except for the systemic cardiac index. Numbers in parentheses indicate mean values. mAoP, mean aortic pressure; mPAP, mean pulmonary artery pressure; NS, non-significant; PVRI, pulmonary vascular resistance index; Qeff, effective cardiac index; Qp, pulmonary cardiac index; Qs, systemic cardiac index; RAP, right atrial pressure; SVRI, systemic vascular resistance index. *p < 0.05 *v* baseline; **p < 0.01 *v* baseline; ***p < 0.001 *v* baseline.

right ventricular dysfunction with preserved left ventricular function, mild to moderate pulmonary insufficiency, and moderate to severe tricuspid regurgitation with maximal velocities consistent with the invasively measured systolic right ventricular pressure at a mean (SEM) of 103 (5) mm Hg. Exercise capacity was limited in all tested patients with maximal oxygen consumption at 15.9 (1.4) ml/kg/min (Weber class B to D). No patient had lung perfusion scan findings suggestive of thromboembolic disease.

Mean (SEM) pulmonary artery pressure in the total cohort at baseline was 68 (4) mm Hg (range 38–105 mm Hg), pulmonary vascular resistance index was 1694 (170) dyne·s·cm^{-5} (range 576–3968 dyne·s·cm^{-5}), systemic vascular resistance index was 2481 (171) dyne·s·cm^{-5} (range 1216–4800 dyne·s·cm^{-5}), and systemic cardiac index was 2.9 (0.2) l/min/m^2 (range 1.1–5.1 l/min/m^2). No adverse effects were noted.

Figure 1 shows in absolute values the effect of BQ-123 on haemodynamic parameters in the total cohort (n = 26). We observed significant decreases in mean pulmonary artery pressure by 6 (2)%, pulmonary vascular resistance index by 19 (2)%, and right atrial pressure by 18 (5)%. There were significant increases in the pulmonary cardiac index by 15 (3)% and effective cardiac index by 10 (3)%. Transpulmonary pressure gradient decreased by 8 (2)%, from 56 to 52 mm Hg (p = 0.01). A marginal, not significant, decrease by 8 (3)%, from 0.68 to 0.63, in the pulmonary to systemic vascular resistance ratio was noted. There was a significant, but within normal limits for the patients' ages, decrease in systemic vascular resistance by 10 (2)% without a decrease in mean arterial pressure. The systemic cardiac index tended to increase by 8 (3)% without reaching significance.

The patients in group 1 with primary or autoimmune PAH (n = 12) responded similarly to the total cohort with significant (p < 0.001) improvement in mean pulmonary artery pressure by 10 (2)%, from 54 to 49 mm Hg, pulmonary vascular resistance index by 20 (3)%, from 1565 to 1239 dyne·s·cm^{-5}, right atrial pressure by 23 (6)%, from 10 to 8 mm Hg, and transpulmonary pressure gradient by 12 (2)%, from 44 to 39 mm Hg. In contrast with the total cohort, in group 1 the systemic cardiac index increased by 12 (4)%, from 2.6 to 2.9 l/min/m^2 (p < 0.05). Systemic vascular resistance index decreased, while remaining within normal limits, by 7 (2)%, from 2661 to 2234 dyne·s·cm^{-5} with stable mean arterial pressure.

The patients in group 2 with PAH caused by congenital heart disease without complete mixing (n = 8) responded with significant (p < 0.05) improvement in pulmonary

Table 2 Effect of BQ-123 infusion in patients with complete mixing

	Saturation aorta (%)		mPAP (mm Hg)		PVRI (dyne·s·cm^{-5})		PVRI/SVRI ratio		Qp (l/min/m^2)		Qs (l/min/m^2)	
Patient	0 min	60 min	0 min	60 min	0 min	60 min	0 min	60 min	0 min	60 min	0 min	60 min
21	70	75	92	83	1824	1344	0.8	0.6	3.7	4.6	3.1	2.6
22	80	86	71	59	704	472	0.6	0.4	6.3	7.6	5.1	3.8
23	84	86	90	90	1864	1552	0.4	0.3	2.8	3.4	2.1	2.0
24	88	88	74	68	672	648	0.5	0.4	6.2	5.8	3.8	3.4
25	95	95	95	91	1888	1168	0.7	0.5	3.6	5.5	2.7	3.0
26	95	95	99	77	2512	1920	1.3	1.0	3.0	3.0	3.7	3.1
Mean (SEM)	85 (4)	87 (3)	87 (5)	78 (5)**	1577 (300)	1184 (223)**	0.7 (0.1)	0.5 (0.1)**	4.3 (0.6)	5.0 (0.7)	3.4 (0.4)	3.0 (0.3)

**p<0.01 *v* baseline.
mPAP, mean pulmonary artery pressure; PVRI, pulmonary vascular resistance index; Qp, pulmonary cardiac index; Qs, systemic cardiac index; SVRI, systemic vascular resistance index.

vascular resistance index by 12 (4)%, from 1976 to 1734 dyne·s·cm^{-5}, pulmonary cardiac index by 18 (7)%, from 2.6 to 3.1 l/min/m^2, and effective cardiac index by 14 (5)%, from 2.6 to 3.0 l/min/m^2. In contrast with the total cohort but in agreement with group 1, in group 2 the systemic cardiac index increased by 14 (5)%, from 2.8 to 3.3 l/min/m^2 ($p < 0.05$). Systemic vascular resistance index decreased, while remaining within normal limits, by 14 (3)%, from 2379 to 2033 dyne·s·cm^{-5}, with stable transpulmonary pressure gradient, mean pulmonary artery, mean arterial, and right atrial pressure.

The patients in group 3 with PAH caused by congenital heart disease with complete mixing or Eisenmenger syndrome ($n = 6$) responded with significant ($p < 0.05$) improvement in mean pulmonary artery pressure by 10 (3)%, from 89 to 78 mm Hg, pulmonary vascular resistance index by 24 (5)%, from 1577 to 1184 dyne·s·cm^{-5}, transpulmonary pressure gradient by 11 (4)%, from 72 to 64 mm Hg, and pulmonary vascular resistance ratio by 26 (4)%, from 0.73 to 0.74. Pulmonary and effective cardiac index, right atrial and mean arterial pressures, and systemic vascular resistance did not change significantly. In contrast with groups 1 and 2, in group 3 the systemic cardiac index tended to decrease by 10 (5)%, from 3.4 to 3.0 l/min/m^2 ($p = 0.06$). Table 2 shows the individual haemodynamic and aortic saturation responses at 60 minutes of BQ-123 infusion in the patients with complete mixing.

As noted above, the main variation in the effect of BQ-123 infusion between the three groups concerned the systemic cardiac index, where a different ($p = 0.0001$, $F = 5.53$) response was observed (fig 2).

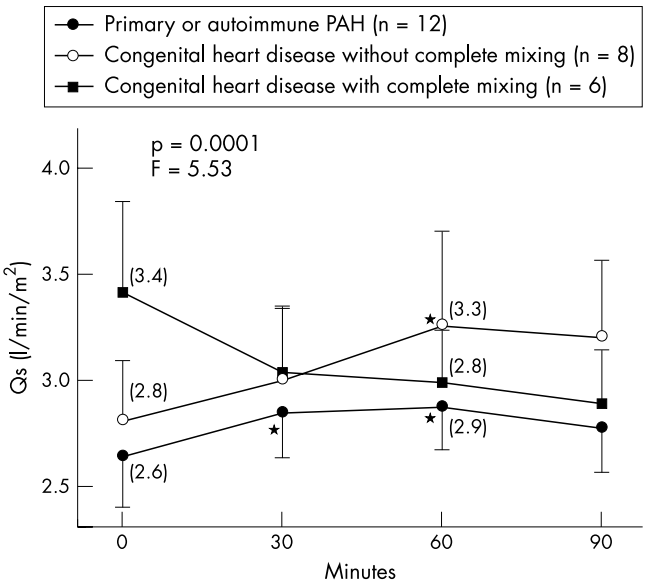

Figure 2 Haemodynamic effect over time of BQ-123 administration on the systemic cardiac index, showing differential effects in the three studied groups.*p<0.05 *v* baseline.

We also analysed the haemodynamic response excluding the complete mixing lesions, therefore the capability for unrestrictive right to left shunt. In four patients (15, 16, 19, and 20), no haemodynamic changes were observed with BQ-123 infusion. In the five responders (2, 5, 7, 10, and 12 in group 1) with normal baseline systemic cardiac index at a mean (SEM) of 3.4 (0.3) l/min/m^2, mean pulmonary artery pressure decreased by 13 (4)%, from 49 (8) to 42 (7) mm Hg, and pulmonary vascular resistance by 16 (6)%, from 901 (274) to 762 (266) dyne·s·cm^{-5}, without a change in their systemic cardiac index. The remaining 11 responders with decreased baseline systemic cardiac index at 2.5 (0.9) l/min/m^2 improved their systemic cardiac index by 21 (11)%, to 3.0 (1.0) l/min/m^2, and their pulmonary vascular resistance by 21 (10)%, from 2006 (901) to 1580 (761) dyne·s·cm^{-5}, without a significant decrease of pulmonary artery pressure.

At baseline in the right atrium, plasma ET-1 concentrations were a mean (SEM) of 3.9 (0.3) ng/l, with a range of 1.9–6.4 ng/l (normal range 1.0–4.5 ng/l). No significant differences between the various sites sampled or changes during BQ-123 infusion were noted. The baseline pulmonary artery to aorta ET-1 ratio was mostly over unity, decreasing significantly after 60 minutes of BQ-123 infusion in the total cohort. This tendency persisted when the patients with complete mixing were excluded (fig 3).

The plasma BQ-123 concentrations in the pulmonary artery increased from 0 at baseline to a mean (SEM) of 250

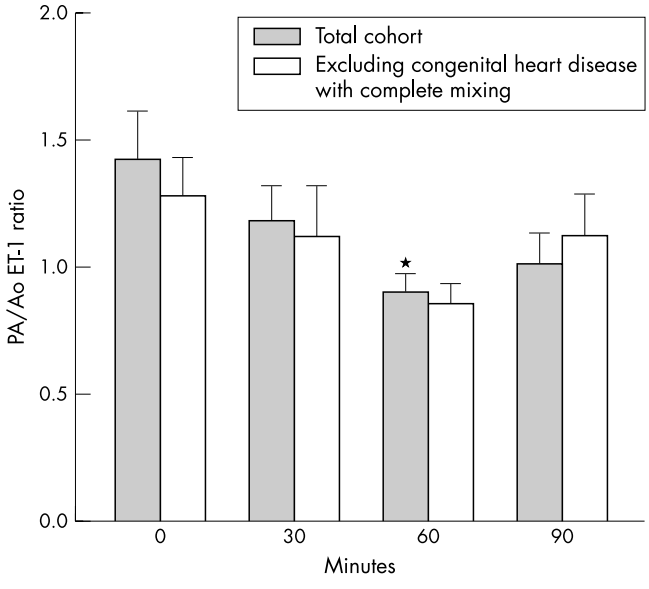

Figure 3 Effect over time of BQ-123 administration on pulmonary to aorta (PA/Ao) endothelin 1 (ET-1) concentration ratio in the total cohort, as well as with the exclusion of patients with complete mixing. *$p < 0.05$ *v* baseline.

(40) nmol at 30 minutes and 236 (51) nmol at 60 minutes of the infusion, decreasing sharply to 67 (40) nmol 30 minutes after the end of the infusion.

DISCUSSION

Our data show that short term continuous intravenous infusion of BQ-123, a selective ET_A receptor antagonist, in patients with severe chronic PAH induced haemodynamic improvement by decreasing pulmonary vascular resistance. Excluding the complete mixing lesions, in patients with normal baseline cardiac index this fall in pulmonary vascular resistance resulted in decreased pulmonary artery pressure, while in patients with decreased baseline cardiac index it led to an improved cardiac index, with or without decreased pulmonary artery pressure. This effect is still important, since the symptoms of severe PAH are partly related to right ventricular failure and the resultant decreased cardiac index. BQ-123 also reduced right atrial pressure and increased systemic cardiac index in the patients with non-complete mixing, thus reflecting the improved right ventricle haemodynamic variables.

Patients with complete mixing lesions and non-reactive increased pulmonary vascular resistance (Eisenmenger syndrome) have a relatively preserved systemic cardiac index at the expense of significant cyanosis. In these patients, a decrease in pulmonary vascular resistance with increased pulmonary cardiac index would be expected to induce a decreased systemic cardiac index but a decreased right to left shunting and improved aortic saturation. Aortic saturation improved over 7% during BQ-123 infusion in patients 21 and 22, our two most cyanotic patients (table 2).

Interestingly, patients 13 and 14 with unoperated atrial septal defects responded similarly to group 2 patients and not to group 3 patients. The observed response may be explained by the presence of an atrial level shunt without unrestrictive communication between the systemic and pulmonary circulation as in group 3 patients, where an increase in pulmonary cardiac index would be associated with a decrease in systemic cardiac index. It is also important to note that, at the end of the study, the pulmonary vascular resistance and pulmonary artery pressure values remained greatly abnormal in all tested patients, despite the observed improvement.

Systemic hypotension with ERA has been reported in two previously published studies in patients with PAH without left heart failure, involving acute administration of high bosentan doses in infants with critical postoperative congenital heart disease[11] and primary or autoimmune PAH.[12] Chronic administration of lower bosentan doses in patients with PAH did not induce systemic hypotension.[13] Previous studies have shown significant systemic effects only with BQ-123 doses $\geqslant$ 300 nmol/min.[17] Systemic vascular resistance decreased within normal limits in our study with stable arterial pressure, possibly because of our patients' stable clinical conditions and the conservative doses administered (200 nmol/min). BQ-123 has a short half life and is rapidly removed from plasma. Hence, a local right atrial infusion in our study may well have maximised delivery to the lung and explains the significant improvement observed in pulmonary haemodynamics.

Previous studies of patients with PAH have reported ET-1 concentrations either higher than those in control subjects, but within normal range[19] or increased without haemodynamic correlations and further increased after administration of a dual ET_A/ET_B antagonist such as bosentan.[12] We found relatively high baseline ET-1 concentrations that did not correlate with haemodynamic parameters or change significantly with BQ-123 infusion. This finding may result from the short period of administration and the absence of interference with ET_B receptors, which have a role in ET-1 clearance.[20] Administration of sitaxsentan, another ET_A receptor antagonist, actually decreased plasma ET-1 concentrations, possibly because of the improved haemodynamics or more available displaced ET-1 for clearance by ET_B receptors.[21] Studies of PAH patients without left heart failure have reported pulmonary to arterial ET-1 ratios both below[19] and close to unity.[5] The pulmonary to arterial ET-1 ratio over unity observed in this study and its decrease with ERA has been reported before[12] and may be caused by displacement of ET-1 from binding sites in the lung.

ERA studies of patients with complete mixing lesions and non-reactive increased pulmonary vascular resistance (Eisenmenger syndrome) have not reported detailed haemodynamic data. The only previous study with ET_A receptor antagonism over 12 weeks involving few patients with congenital heart disease[14] showed no short term effect or long term change in cardiac output despite the improved pulmonary vascular resistance, pulmonary artery pressure, and exercise capacity. Both findings may be due to the heterogeneity of the population and analysis of the data irrespective of the presence and degree of mixing, which influences the ratio of pulmonary to systemic cardiac output. Our patient population with complete mixing was limited; however, acute ET_A receptor antagonism in these patients was more selective to the pulmonary circulation. This was shown by the improved pulmonary to systemic vascular resistance ratio, pulmonary and effective cardiac index, and pulmonary vascular resistance, without greater reduction in systemic vascular resistance, which would lead to increased right to left shunting and cyanosis. Aortic saturation tended to increase in the more cyanotic patients as a result of the more favourable pulmonary haemodynamics.

Chronic prostacyclin treatment is associated with considerable inconvenience and morbidity[22] but its clinical benefits are independent of its short term pulmonary vasodilatator effect. ERA may be similar in benefit, since in animal studies it has been shown to prevent and reverse PAH and promote pulmonary vascular remodelling.[23] The acute effects of ERA were not only maintained but were also more pronounced during prolonged treatment in the case of heart failure[10] and were sustained over 12 weeks in the case of primary or autoimmune PAH.[13] The same long term improvement may well be encountered with ET_A receptor antagonism in chronic PAH of diverse pathophysiology, as was shown in one previous study including a few congenital heart disease patients.[14] A chronic improvement of 11–26% in pulmonary vascular resistance and cardiac index, as encountered in our responders, may be expected to reduce symptoms and benefit this population in the long term; however, this assumption can only be proved with further studies.

Study limitations

This study has the limitations of an acute evaluation without long term data and the relatively small sample size of patients with PAH of diverse aetiology. The wide age range may also affect the underlying disease process and the response to ERA. The study is based on calculated haemodynamic measurements, the validity of which may be influenced by factors such as use of assumed oxygen consumption values. Like other studies in this field of work, ours did not compare the effect of ET_A receptor antagonism with that of other vasoactive agents. Such comparisons have been published in animal models showing that ERA produces more potent pulmonary vasodilatation than nitric oxide inhalation alone, better endothelium dependent vasodilatation, and increased pulmonary vascular smooth muscle sensitivity to nitric oxide.[24] In a small study of acute PAH involving sequential 60 minute administration of BQ-123 and prostacyclin, we have reported that patients responded differently to each drug, possibly because of the diverse pathophysiology of PAH and the different mechanisms of action of the two agents.[25] Against these limitations, this is a study with detailed haemodynamic analysis of the effect of selective ET_A receptor antagonism in diverse aetiology PAH that, importantly, involves less studied populations, such as patients with congenital heart disease.

Conclusion

This study showed that acute ET_A receptor antagonism induces haemodynamic improvement in patients with severe chronic PAH that is primary or autoimmune, as well as PAH related to congenital heart defects with or without complete mixing. Additional detailed studies with long term ERA, especially in more poorly studied groups such as those with congenital heart disease, are needed to determine whether the observed effects are sustained and whether chronic oral ERA may have a role in the treatment of PAH of diverse aetiology.

Authors' affiliations
S C Apostolopoulou, S Rammos, Department of Paediatric Cardiology, Onassis Cardiac Surgery Centre, Athens, Greece
Z S Kyriakides, D Th Kremastinos, 2nd Department of Cardiology, Onassis Cardiac Surgery Centre
D J Webb, N R Johnston, Department of Medical Sciences, University of Edinburgh, Western General Hospital, Edinburgh, UK
D V Cokkinos, 1st Department of Cardiology, Onassis Cardiac Surgery Centre

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